PATENT ABSTRACTS OF JAPAN

(11)Publication number : 10-237102
(43)Date of publication of application : 08.09.1998

(51)Int.Cl. C08B 15/05
A61L 33/00

(21)Application number : 09-046391
(22)Date of filing : 28.02.1997

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(54) SOLUBLE CELLULOSE DERIVATIVE AND ITS APPLICATION

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a soluble cellulose derivative usable as a bio-compatible material in a high yield and high quality by combining a soluble cellulose derivative with a phosphorylchloine group-containing polymer with an epoxy group.
SOLUTION: The objective derivative is obtained by reacting (A) a soluble cellulose (e.g. hydroxypropylmethylcellulose) with (B) a copolymer containing constituting units of (i) a phosphorylcohline group-containing monomer [e.g. 2-(meth)acryloyloxyethyl-2'-(trimethylammonio)ethylphosphate] and (ii) an epoxy group-containing monomer (e.g. glycidylmethacrylate) in the presence of a solvent (e.g. nitromethane) at a temp. of 10-100°C for 1-100hr. A bio-compatible material comprising the derivative is excellent in safety, has compatibility with blood and affinity to cellulose membrane, and especially has anti-thrombogenic property. This material can be applied, for example, to the surface, etc., of a base of a medical material such as a hemodialysis membrane material.

LEGAL STATUS
[Date of request for examination] 04.08.2003
[Date of sending the examiner's decision of rejection]
[Kind of final disposal of application other than the

examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the biocompatible mater which used a fusibility cellulosic and it.
[0002]
[Description of the Prior Art] Celluloses are naturally-ocurring polymers which use a seed fiber, a gin hide, wood, etc. as a raw material, and are widely used in the industrial field which manufactures fiber, plastics, paper manufacture, etc. The fault which a cellulose has is improved, and since plasticity is given while becoming fusibility to water and an organic solvent, the fusibility cellulose obtained according to partial esterification or the etherification of three hydroxyl groups of a D-glucopyranose unit whose cellulose is a configuration unit is used for broad applications, such as sizing of a dyeing-and-weaving object and paper, a sizing compound, a thickener, an extending agent, glazing, a latex paint, a coating remover, drugs, and cosmetics.
[0003] On the other hand, the cellulose is very useful also as a medical ingredient. The regenerated-cellulose film which reproduced especially the cellulose by the copper ammonium method was widely used as a material of the hemodialysis film, and has played the big role in a renal failure patient's prolongation of life, and social rehabilitation with the advance of a dialyzer and a dialysis technique. This is exactly because it has the high safety supported by the old track record while having the dialysis engine performance and a mechanical strength excellent in the regenerated-cellulose film.
[0004] However, in spite of the advance of dialysis, the various problems accompanying dialysis are still unsolved, and are left behind. There is a problem of the various side effects considered to be generated in one of them over a long period of time [of an anticoagulant] for extensive administration. When performing artificial dialysis conventionally, in order to control the blood-clotting reaction within an artificial dialysis machine, repetitive administration of the anticoagulant represented by heparin has been performed. However, the solute removal engine performance of an artificial dialysis machine is improved, and the problem by using current [to which the long-term prolongation of life which is going to reach in 20 is attained], and heparin has been pointed out one after another. Especially, extension or the allergic response of liver failures, such as disorder of lipid metabolism by prolonged administration of heparin, and bleeding time is accepted as a side effect to a patient. or [reducing the amount of the anticoagulant used from such a viewpoint in the case of an artificial dialysis therapy] -- or development

of the artificial dialysis machine which does not cause blood coagulation even if it does not use it at all is pressing need.

[0005] The attempt which improves the regenerated-cellulose film until now is performed paying attention to control of the transient leukopenia and complement-activity-izing when the regenerated-cellulose film performs hemodialysis, and although the giant molecule which has the 3rd class amino group is fixed to a front face or the approach to which a front face is made to carry out covalent bond of the hydrophilic giant-molecule chains, such as a polyethylene oxide chain, is reported, it is mainly inadequate about control of blood coagulation. On the other hand, the engine performance which was excellent in everything but the regenerated-cellulose film is not spoiled, but the method of improving anti-thrombus nature is also proposed. For example, although the approach of giving anti-thrombus nature by heparinizing a film front face is proposed by JP,51-194,A, since sufficient effectiveness is not acquired and cost also becomes comparatively high-priced, it is not put in practical use.

[0006] By the way, the attempt using a phospholipid polar group as an approach of giving haemocompatibility to the regenerated-cellulose film also occurs, for example, 2-methacryloiloxy-ethyl phosphorylcholine (it abbreviates to MPC) is proposed by JP,54-63025,A. This macromolecule front face is similar to the biomembrane, and a front face is not adsorbed in plasma protein, but it is being thought of because induction of adhesion of a platelet, the activation, etc. is not carried out that the macromolecule which has the phosphorylcholine radical which is a phospholipid polar group controls blood coagulation effectively (a biomaterial, 8,231-237 (1990), J.Biomed.Mater.Res., 25, 1397-1407 (1991)).

[0007] It is indicated by JP,3-39309,A that the copolymer of a phosphorylcholine radical content monomer, and the methacrylic ester and styrene in which a polymerization is possible is extremely excellent in anti-thrombus nature, and how to fix this copolymer to the regenerated-cellulose system film is also considered. However, since compatibility with a cellulose is low inferior to adhesion, in coating, these phosphorylcholine radical content polymers have omission from a cellulose front face, and worries about elution, and do not fit the reforming. Cerium ion is used for a radical polymerization initiator, the approach of carrying out the graft copolymerization of the MPC to a cellulose is indicated by JP,5-220218,A, and it is shown in it that the biocompatibility which was excellent by fixing to a regenerated-cellulose system film front face can be discovered. However, by this approach, strong toxic cerium ion is used, it removes and, in the long-term use to a ****** sake, a problem remains on a point [safety].

[0008] From a viewpoint that make a macromolecule chain react or the approach of carrying out a graft stops omission and elution to a base material on the other hand, it is effective and there is a technique (BIO INDUSTRY, 8 (6), 412-420 (1991)) of carrying out the graft polymerization of the MPC to a cellulose wall, as a well-known technique. However, reaction actuation becomes very complicated in order that this approach may remove that a cellulose wall must be put on the bottom of an anoxia ambient atmosphere at the time of a polymerization, and the cerium ion used as a polymerization initiator from a cellulose wall. Moreover, there is diffusibility in MPC, since even Uchibe of pore enters and a reaction occurs in the whole film, membranous penetrable ability falls, or the film receives damage with cerium ion, a mechanical strength falls, or a reaction advances to an ununiformity, and there is a problem that dispersion arises in adhesion control of a platelet. The reforming approach of the cellulose which introduces into a cellulose wall the copolymer of the monomer which has MPC, methacrylic ester, and a carboxyl group by the ester bond is indicated by JP,7-231935,A. However, since the reaction in this approach is a dehydration condensation reaction between the macromolecules of a

reactant low cellulose hydroxyl group and the carboxyl group in a copolymer, it needs the dehydrating agent of an overlarge, and a severe reaction condition. For this reason, a bad influence is done, or removal of a reaction reagent or a resultant becomes difficult, and existence of little water cannot demonstrate sufficient engine performance, and, moreover, is not suitable as a industrial process from an economical field. JP,7-184989,A -- (i) MPC -- and -- an epoxy group -- content -- a monomer -- a copolymer -- the amino group -- and -- a carboxyl group -- inside -- at least -- one side -- a radical -- two -- a piece -- more than -- having -- a compound -- having constructed the bridge -- polymeric materials -- or -- (-- ii --) -- MPC -- the amino group -- content -- a monomer -- and -- a carboxyl group -- content -- a monomer -- inside -- at least -- one side -- a monomer -- a copolymer -- an epoxy group -- two -- a piece -- more than -- having -- a compound -- having constructed the bridge -- polymeric materials -- either -- a base material -- a front face -- having covered -- medicine -- an ingredient -- indicating -- having -- **** . Moreover, since this medical ingredient discovers the outstanding haemocompatibility and the covered polymeric materials do not drop out easily, it is also indicated that haemocompatibility is held over long duration at stability. However, when the permeable membrane front face of an artificial dialysis machine is coated with the polymeric materials which carried out [above-mentioned] bridge formation, gel generates on a film front face and the remarkable fall of the penetrable ability of coating unevenness or the film is caused. Moreover, covering a base material front face with a copolymer with at least one kind of monomer among MPC, an epoxy group content monomer, a hydroxyl-group content monomer and an amino-group content monomer, and a carboxy group content monomer is indicated by JP,7-184990,A. However, when this system also applies the above-mentioned copolymer to the permeable membrane of an artificial dialysis machine, since bridge formation immobilization is carried out on a base material front face, gel generates this copolymer on a film front face, and the problem of causing the remarkable fall of the penetrable ability of coating unevenness or the film is not avoided.

[0009]

[Problem(s) to be Solved by the Invention] The 1st purpose of this invention is to offer the fusibility cellulosic which can be used for the biocompatible mater which can solve the above-mentioned problem. Moreover, the 2nd purpose of this invention is to offer the biocompatible mater suitable for the ingredient which is excellent in safety, and has the both sides of haemocompatibility and the compatibility over a cellulose wall, and has especially anti-thrombus nature.

[0010]

[Means for Solving the Problem] The fusibility cellulose and the phosphorylcholine radical content polymer which is the outstanding biocompatible mater which has phospholipid similar structure were combined by the reactant high epoxy group, and in the cellulosic excellent in biocompatibility, it was quality, and this invention persons came examination in piles variously, in order to obtain, high yield and. However, since both reaction was a macromolecule reaction to which reactivity falls remarkably, said copolymer was not able to be made to introduce into a fusibility cellulose by the chemical bond in fact by limiting upwards the solvent which may dissolve both a fusibility cellulose and a phosphorylcholine radical polymer. For example, when hydroxyethyl cellulose and the phosphorylcholine radical content copolymer containing an epoxy group were made to react to the bottom of alkali existence in a water solution, the fusibility cellulosic to which the ring opening reaction of the epoxy group by water gives priority and which is made into the purpose was not obtained. It came to complete a header and this invention for reacting efficiently and the fusibility cellulosic with which said copolymer was introduced into the fusibility cellulose which is not known conventionally by

covalent bond being obtained, as a result of making a fusibility cellulose and the phosphorylcholine radical content polymer containing an epoxy group react to the bottom of basic catalyst existence by the non-drainage system as a result of repeating research wholeheartedly about the system of reaction for example, in a non-drainage system there, and this derivative having the remarkable engine performance. That is, according to this invention, the fusibility cellulosic which the copolymer (B) including the configuration unit of a fusibility cellulose (A), and a phosphorylcholine radical content monomer (b1) and an epoxy group content monomer (b2) was made to react, and was obtained and with which said copolymer (B) was introduced into said fusibility cellulose (A) by covalent bond is offered. Moreover, according to this invention, the biocompatible mater characterized by consisting of said fusibility cellulosic is offered.

[0011]

[Embodiment of the Invention] The fusibility cellulosic of this invention is the compound which the copolymer (B) including the configuration unit of a fusibility cellulose (A), and a phosphorylcholine radical content monomer (b1) and an epoxy group content monomer (b2) was made to react, and introduced the copolymer (B) into the fusibility cellulose (A) by covalent bond. As a fusibility cellulose (A) used by this invention, methyl cellulose, ethyl cellulose, cellulose acetate, a nitrocellulose, a carboxymethyl cellulose, carboxy methyl ethyl cellulose, hydroxyethyl cellulose, hydroxypropylcellulose, ethyl hydroxyethyl cellulose, the hydroxypropyl methylcellulose (HPMC), etc. are mentioned.

[0012] The phosphorylcholine radical content monomer (b1) which forms the configuration unit of the copolymer (B) used for this invention is a monomer which has a vinyl group and a phosphorylcholine radical. Specifically, 2-(meta) acryloyloxyethyl-2'-(trimethylammonio) ethyl phosphate, 2-methacryloyloxy ethoxyethyl phosphorylcholine, 6-methacryloyloxy hexyl phosphorylcholine, 10-methacryloyloxy ethoxy nonyl phosphorylcholine, allyl compound phosphorylcholine, butenyl phosphorylcholine, hexenyl phosphorylcholine, OKUTE nil phosphorylcholine, decenyl phosphorylcholine, etc. are mentioned. These phosphorylcholine radical content monomers (b1) can be used as independent or mixture. From points, such as availability, 2-(meta) acryloyloxyethyl-2'-(trimethyl ANIMONIO) ethyl phosphate (MPC) is mentioned preferably. 20 - 95-mol [5 - 99.9-mol %, especially]% of the content rate of the configuration unit of a phosphorylcholine radical content monomer (b1) is desirable in the copolymer (B) of this invention. When the mole ratio of the configuration unit of a monomer (b1) makes it a biocompatible mater in the case of below 5 mol %, it is not fully discovered and biocompatibility and haemocompatibility are not desirable. On the other hand, if 99.9-mol % is exceeded, since the content of the epoxy group in a copolymer will become less than [0.1 mol %] inevitably and the problem mentioned later will arise, it is not desirable.

[0013] The epoxy group content monomer (b2) which forms the configuration unit of the copolymer (B) used for this invention is a monomer which has a vinyl group and an epoxy group at least. Specifically, glycidyl acrylate, glycidyl methacrylate (GMA), methyl glycidyl methacrylate, allyl glycidyl ether, etc. are mentioned. These epoxy group content monomers (b2) can be used as independent or mixture. 1 - 20-mol [0.1 - 30-mol %, especially]% of the content rate of the configuration unit of an epoxy group content monomer (b2) is desirable in the copolymer (B) of this invention. If in the case of below 0.1 mol % the introductory reaction to a fusibility cellulose (A) stops being able to happen easily and the mole ratio of the configuration unit of a monomer (b2) exceeds 30-mol %, in order that bridge formation between copolymers and between a copolymer and a cellulose may become easy to take place and gel

may generate, it is not desirable in the case of the reaction of a fusibility cellulose (A) and a copolymer (B).
[0014] The copolymer (B) of this invention may have said monomer (b1) and (b2) the configuration unit of an except as a configuration unit. As a monomer for forming a monomer (b1) and (b2) the configuration unit of an except Although it is other monomers in which a radical polymerization is possible, and it is not limited especially unless the effectiveness of this invention is spoiled For example, a methyl acrylate (meta), an ethyl acrylate (meta), acrylic-acid (meta) propyl, Butyl acrylate, acrylic-acid (meta) hexyl, acrylic-acid (meta) lauryl, (Meta) Acrylic ester (meta) monomers, such as acrylic-acid stearyl; (meta) Acrylic-acid-2-hydroxyethyl, (Meta) (Meta) acrylic-acid (meta) hydroxyalkyl ester monomers [, such as 2-hydroxypropyl acrylate,]; (meta) -- acrylic-acid amide; -- styrene -- Styrene monomers, such as methyl styrene and permutation styrene; Ethyl vinyl ether, vinyl ether monomers [, such as butyl vinyl ether,]; -- N-vinyl-pyrrolidone; -- a vinyl chloride -- A vinylidene chloride, ethylene, a propylene, unsaturated hydrocarbon system monomers, such as an isobutylene, or permutation unsaturated hydrocarbon system monomer; -- acrylonitrile; -- glycosyl ethyl methacrylate (GEMA); -- oligo ethylene glycol methacrylate; -- polyethylene glycol monomethacrylate etc. is mentioned. These monomers may mix and use one sort or two sorts or more. in order that the content rate of the configuration unit of other monomers in said copolymer (B) may not spoil the solubility over the water of the fusibility cellulosic obtained -- less than [60 mol %] -- less than [50 mol %] is especially desirable.
[0015] In order to prepare a copolymer (B), it is obtained by carrying out the polymerization of the monomer constituent which contains other monomers if needed to said phosphorylcholine radical content monomer (b1) and an epoxy group content monomer (b2) under polymerization initiator existence and in a solvent. Especially a polymerization initiator is not limited but the usual polymerization initiator for radical polymerizations etc. is used. Specifically Benzoyl peroxide, t-butylperoxy2-ethylhexanoate, Succinyl peroxide, glutar peroxide, a succinyl peroxy GURUTA rate, t-butyl par OKISHIMA rate, t-butylperoxy perpivalate, Organic peroxide, such as G 2-ethoxyethyl peroxy carbonate, 3-hydroxy-1, and 1-dimethyl butylperoxy pivalate; Azobisisobutyronitril, Dimethyl -2, 2-azobisisobutyrate, 1-(1-cyano-1-methylethyl) (azo) formamide, 2 and 2-azobis (2-methyl-N-phenyl propionamidin) dihydrochloride, 2 and 2-azobis (2-methyl-N -(2-hydroxyethyl)- propione amide), Azo compounds, such as 2 and 2-azobis (2-methyl propione amide) JIHAIDO rate, 4 and 4, - azobis (4-cyano pentanoic acid), 2, and 2-azobis (2-(hydroxymethyl) propionitrile), are mentioned. These polymerization initiators can be used as independent or mixture on the occasion of use.
[0016] As a solvent in the case of manufacturing a copolymer (B), a methanol, ethanol, propanol, a butanol, benzene, toluene, a tetrahydrofuran, dioxane, dichloromethane, chloroform, or these mixed solvents are mentioned, for example.
[0017] As for the number average molecular weight of said copolymer (b), 5000-300000 are desirable. When number average molecular weight is less than 5000, the number of the epoxy groups per molecule decreases, and the installation to a fusibility cellulose becomes difficult. Moreover, since solution viscosity will become high and the bridge formation object between copolymers and a cellulose, and a copolymer will become handling is difficult, and is easy to be formed in case it is a reaction with a fusibility cellulose if number average molecular weight exceeds 300000, it is not desirable. The fusibility cellulosic of this invention is obtained by making it react so that said copolymer (B) may be introduced into said fusibility cellulose (A) by covalent bond. As for especially a fusibility cellulose (A),

it is desirable to use it, making it dissolve in a solvent so that it may become 1 - 10 % of the weight 0.1 - 20 % of the weight of concentration in said reaction. Moreover, as for the percentage of functional groups, such as a hydroxyl group of a fusibility cellulose (A), and the epoxy group in a copolymer (B), i. e., the percentage of a functional group/epoxy group, 0.1/100:1 especially 1 / 1 - 10/1 are desirable in a reaction solvent at a mole ratio. [1-100:1] When the epoxy group to said functional group 0.1 exceeds 1, bridge formation between both macromolecules is easy to happen and is not desirable. Moreover, when the epoxy group to said functional group 100 is less than one, a reaction stops being able to happen easily. As for said reaction, it is desirable to carry out to the bottom of basic catalyst existence preferably. As a basic catalyst, although a dimethylamino pyridine, a pyridine, triethylamines, or such mixture are mentioned, when reactivity is taken into consideration, a dimethylamino pyridine is the most desirable. The charge of a basic catalyst has the desirable amount from which the D-glucopyranose unit of a basic catalyst:fusibility cellulose (A) is set to 1:1-1:50 by the mole ratio.

[0018] although the reaction of said copolymer (B) and fusibility cellulose (A) can be performed under solvent existence -- as a solvent -- except water and low-molecular alcohol -- it is -- an epoxy group -- receiving -- inactive -- it is -- and a fusibility cellulose (A) and a copolymer (B) -- both -- or it is altogether available if it is the solvent which may dissolve a copolymer (B). Specifically, nitromethane, nitroethane, etc. are mentioned. The range of 1 - 100 hours has [the reaction condition of a fusibility cellulose (A) and a copolymer (B)] desirable reaction time at the reaction temperature of 10-100 degrees C. When a reaction cannot occur easily, reaction temperature exceeded 100 degrees C at less than 10 degrees C and a long duration reaction is carried out, since decomposition of MPC is promoted, it is not desirable. Although covalent bond of a fusibility cellulose (A) and the copolymer (B) is carried out by this reaction, chemical bonds, such as ether linkage, are mentioned as covalent bond.

[0019] As for the molecular weight of the fusibility cellulosic of this invention, 10000-1 million are desirable at number average molecular weight. Since solubility will worsen if adhesion [as opposed to a base material in molecular weight] is bad and exceeds 1 million, it is not desirable at less than 10000.

[0020] The biocompatible mater of this invention can be used by the approach which becomes substantial from said fusibility cellulosic, for example, contacts the base material front face of various medical ingredients, such as a hemodialysis film ingredient, etc., and it is made to dry. For example, what is necessary is to dissolve a biocompatible mater in a solvent, to make a cellulose wall contact, and just to make it dry as covering film, in order to give the biocompatible mater of this invention to a cellulose wall in manufacturing the hemodialysis film. As this solvent, fundamentally, if it is the solvent which may dissolve a fusibility cellulosic, it is altogether available. A suitable solvent must be chosen in consideration of the safety at the time of remaining in a minute amount in the ease of carrying out of removal etc. As concentration of a fusibility cellulosic, the concentration of the biocompatible mater made to dissolve in this solvent has the desirable range of 0.005 - 5 weight / capacity %, and its range of 0.01 - 1 weight / capacity % is still more desirable. Since the homogeneity of a coat will cause [of the variation in the engine performance, or the biocompatible mater at the time of use] omission difficult to get if the concentration of a fusibility cellulosic exceeds 5 weight / capacity %, it is not desirable. In order to make it dry and to remove a solvent, after a solvent washes the film which is performed by the usual approaches, such as a vacuum drying, draught drying, and stoving, when a solvent is volatility, and is obtained if needed when a solvent is a high-boiling point comparatively, it can carry out by a solvent and an volatile organic solvent with sufficient compatibility washing, and drying like the above. As an amount of a fusibility cellulosic, the amount of the biocompatible mater which a cellulose wall is made

to fix has the desirable range of 2 cm 1-100microg /, and especially its range of 5-50microg/cm2 is desirable. When the amount of the fixed fusibility cellulosic is less than two 1microg/cm, since the dialysis engine performance will worsen if sufficient anti-thrombus nature is not demonstrated but 100microg/cm2 is exceeded, it is not desirable.

[0021]

[Effect of the Invention] Since the fusibility cellulosic of this invention is excellent in safety and has the both sides of haemocompatibility and the compatibility over a cellulose wall, it is suitable as an ingredient which gives anti-thrombus nature to the regenerated-cellulose system film currently used for the artificial dialysis machine. Moreover, since the biocompatible mater which consists of said fusibility cellulosic does not drop out easily [it is uniform on a regenerated-cellulose system film front face, and / in order to form a uniform coating layer, membranous penetrable ability is maintained for a long period of time, and], it can demonstrate anti-thrombus nature over a long period of time.

[0022]

[Example] Next, an example explains the contents of this invention to a detail further. The parameter indicated in the following synthetic examples was respectively measured by the following approach.
(1) 6mg of monomer configuration presentation (1-1) MPC unit content MPC content copolymers of a copolymer is dissolved in 10ml ethanol, and 50micro of this solution l is made to harden by drying at 75 degrees C. Next, organic phosphorus is decomposed into inorganic phosphorus by adding 260micro of 70% of the weight of perchloric acid l, and heating for 20 minutes at 180 degrees C. 1.9ml of distilled water, 0.4ml of 1.25% of the weight of ammonium molybdates, and 0.4ml of 5% of the weight of ascorbic acids are added after cooling, and it warms for 5 minutes and is made to color at 100 degrees C. Next, the quantum of the Lynn concentration is carried out by measuring the absorbance in 817.8nm of this solution. In addition, a calibration curve is created using disodium hydrogenphosphate. From this value, the content of Lynn in a copolymer is calculated and this computes the MPC content in a copolymer (mol %).

[0023] (1-2) Add 3g of isopropanol solutions of an MPC content copolymer to 15g (pH=7.3) of 0.2M sodium-thiosulfate 50 capacity % isopropanol water solutions containing a glycidyl methacrylate (GMA) unit content phenolphthalein 10% of the weight, and a solution presents purple by carrying out heating churning on a stirrer. The content of an epoxy group is calculated from the amount of the acetic acid which neutralized by adding 0.2-N acetic-acid water solution one by one, carried out the back titration of the produced purple solution in 0.02-N sodium-hydroxide water solution, and consumed it. From this value, the GMA content in a copolymer (mol %) is computed.

[0024] (2) Present GPC measurement after carrying out filter (0.8 micrometers) filtration of the 1-% of the weight solution of the number-average-molecular-weight MPC content copolymer of an MPC content copolymer. Ethanol is used as an eluate. The number average molecular weight of an MPC content copolymer is calculated by polyethylene-glycol conversion.

[0025] Example of <composition of MPC content polymer> composition 1MPC39.01g (95-mol %) and GMA0.99g (five-mol %) were dissolved in isopropanol 358g, and nitrogen gas fully permuted the inside of a reaction container. 2.18g (mol of the peroxide contained in this number:2.50mmol) of toluene solutions of 20% of the weight of t-butylperoxy perpivalate was added to this solution, it was immersed during the 60-degree C hot bath, and the heating polymerization was carried out for 5 hours. The reaction solution was dropped into diethylether after cooling, and the vacuum drying of the obtained copolymer was carried out the back according to **. The content of the phosphorylcholine radical

content monomeric unit in the obtained copolymer and an epoxy group content monomeric unit and the number average molecular weight of a copolymer are shown in Table 1.

[0026] The copolymer was obtained like the synthetic example 1 except having replaced the operating rate of synthetic example 2 each monomer with MPC37.97g (90-mol %) and GMA2.03g (ten-mol %). The content of the phosphorylcholine radical content monomeric unit in the obtained copolymer and an epoxy group content monomeric unit and the number average molecular weight of a copolymer are shown in Table 1.

[0027] The copolymer was obtained like the synthetic example 1 except having replaced the operating rate of synthetic example 3 each monomer with MPC35.70g (80-mol %) and GMA4.30g (20-mol %). The content of the phosphorylcholine radical content monomeric unit in the obtained copolymer and an epoxy group content monomeric unit and the number average molecular weight of a copolymer are shown in Table 1.

[0028] a synthetic example 4 use monomer -- MPC -- the polymer was obtained like the synthetic example 1 except having replaced with independently 40.00 g (135mmol). The number average molecular weight of the obtained polymer is shown in Table 1.

[0029] Synthetic example 5MPC2.0g (35-mol %), GMA0.14g (five-mol %), 1.65g [of n-butyl methacrylate] (BMA) (60-mol %), and azobisisobutyronitril (azobisuisobutironitoriru) 0.04g was dissolved in ethanol 28ml, and argon gas permuted the inside of a reaction container enough. The polymerization reaction was performed by immersing this reaction container during a 60-degree C hot bath for 24 hours. Actuation of having filled chloroform with a polymerization solution and settling a copolymer was repeated twice after cooling, and after replacing the last with chloroform, settling it with ethyl ether and carrying out precipitate of a copolymer a ** exception, it obtained the copolymer given in JP,7-184989,A by carrying out a vacuum drying. Yield was 90%. The content of the phosphorylcholine radical content monomeric unit in the obtained copolymer and an epoxy group content monomeric unit and the number average molecular weight of a copolymer are shown in Table 1.

[0030] The copolymer given in JP,7-184989,A was obtained like the synthetic example 5 except having replaced synthetic example 6 each use monomer with MPC2.0g (35-mol %), allylamine 0.06g (five-mol %), and 1.65g (BMA) (60-mol %) of n-butyl methacrylates. Yield was 88%. The content of the phosphorylcholine radical content monomeric unit in the obtained copolymer and an amino-group content monomeric unit and the number average molecular weight of a copolymer are shown in Table 1.

[0031] The copolymer given in JP,7-184989,A was obtained like the synthetic example 5 except having replaced synthetic example 7 each use monomer with MPC2.0g (35-mol %), methacrylic-acid (MA) 0.08g (five-mol %), and BMA1.65g (60-mol %). Yield was 70%. The content of the phosphorylcholine radical content monomeric unit in the obtained copolymer and a carboxyl group content monomeric unit and the number average molecular weight of a copolymer are shown in Table 1.

[0032] The copolymer given in JP,7-184990,A was obtained like the synthetic example 5 except having replaced synthetic example 8 each use monomer with MPC2.0g (35-mol %), GMA0.03g (one-mol %), BMA1.52g (55-mol %), and 2-hydroxyethyl methacrylate 0.22g (nine-mol %). Yield was 95%. The content of the phosphorylcholine radical content monomeric unit in the obtained copolymer, an epoxy group content monomeric unit, and a hydroxyl-group content monomeric unit and the number average molecular weight of a copolymer are shown in Table 1.

[0033] The copolymer given in JP,7-184990,A was obtained like the synthetic example 5 except having replaced synthetic example 9 each use monomer with MPC2.0g (35-mol %), GMA0.03g (one-mol %),

BMA1.52g (55-mol %), and acrylamide 0.125g (nine-mol %). Yield was 60%. The content of the phosphorylcholine radical content monomeric unit in the obtained copolymer, an epoxy group content monomeric unit, and an amino-group content monomeric unit and the number average molecular weight of a copolymer are shown in Table 1.

[0034] The copolymer given in JP,7-184990,A was obtained like the synthetic example 5 except having replaced synthetic example 10 each use monomer with MPC2.0g (35-mol %), GMA0.03g (one-mol %), BMA1.52g (55-mol %), and 0.127g (nine-mol %) of acrylic acids. Yield was 70%. The content of the phosphorylcholine radical content monomeric unit in the obtained copolymer, an epoxy group content monomeric unit, and a carboxyl group content monomeric unit and the number average molecular weight of a copolymer are shown in Table 1.

[0035] After putting MPC8.88g (24.9-mol %), methacrylic-acid (MA)0.35g (3.4-mol %), 2-(ethylhexyl) methacrylate 17.16g (71.7-mol %), and azobisuisobutironitoriru97.8mg into the ampul for synthetic example 11 glass polymerizations and adding ethanol 120ml, argon gas fully permuted the inside of a reaction container. Ampul was sealed and the 60-degree C oil bath was made to put in and carry out the heating polymerization of this for 3 hours. After having dropped reaction mixed liquor into diethylether after cooling, settling the copolymer and carrying out churning washing, the copolymer given in JP,7-231935,A was obtained by collecting and carrying out a vacuum drying. The content of the phosphorylcholine radical content monomeric unit in the obtained copolymer and a carboxyl group monomeric unit and the number average molecular weight of a copolymer are shown in Table 1.

[0036]

[Table 1]

合成例	ホスホリルコリン基含有単量体単位含有量 (モル%)	エポキシ基含有単量体単位含有量 (モル%)	アミノ基含有単量体単位含有量 (モル%)	水酸基含有単量体単位含有量 (モル%)	カルボキシル基含有単量体単位含有量 (モル%)	数平均分子量
1	96	4	—	—	—	25000
2	92	8	—	—	—	25000
3	82	18	—	—	—	27000
4	100	—	—	—	—	24000
5	34. 4	4. 5	—	—	—	63000
6	35. 4	—	4. 2	—	—	45000
7	35. 5	—	—	—	5. 5	71000
8	34. 4	1. 7	—	9. 9	—	56800
9	35. 3	1. 3	8. 9	—	—	61200
10	34. 5	1. 0	—	—	9. 7	57600
11	25	—	—	—	3	42000

[0037] HPMC1g (they are 4.92mmol(s) at a D-glucopyranose unit) and 4-(N and N-dimethylamino) pyridine 0.2g (1.64mmol) were supplied to <manufacture of haemocompatibility fusibility cellulosic> example 1-1 - 1-3 nitromethane 19g under churning, and it agitated at the room temperature for 1 to 2 hours. Subsequently, 5g of each copolymers obtained in the synthetic examples 1-3 was added, and it was immersed after the churning dissolution and during the hot bath at 50 degrees C, and was made to react for 24 hours, respectively. The reaction solution was dropped into ethanol after cooling, the resultant was settled, and churning washing was fully carried out. Then, the vacuum drying was carried out, after carrying out the ** exception and removing an unreacted copolymer. It dissolved in each

heavy water (D2O) by making the resultant which is the obtained fusibility cellulosic into an example 1-1 to 1-3, respectively, and when 1 H-NMR measurement was carried out, the peak which originates in MPC in addition to the peak which originates in HPMC in all samples was also observed. It has been checked that the copolymer obtained in the synthetic examples 1-3 had been introduced into HPMC by covalent bond from this result.

[0038] According to the approach of an example 1-1 to 1-3, it reacted using the polymer obtained in the example 4 of example of comparison 1-1 composition. Although 1 H-NMR analyzed the obtained reactant, the peak originating in MPC was not accepted.

[0039] Rinsing and the cellulose film (10cmx10cm) which carried out the air dried were made beforehand immersed in 1 weight / capacity % water solution of each MPC content fusibility cellulosic obtained in the <manufacture of haemocompatibility regenerated-cellulose system film> example 2-1 - 2-3 example 1-1 to 1-3 for 10 minutes, respectively. Then, it dried in room temperature atmospheric air, and the vacuum drying was performed further. Coating processing was again performed on the above-mentioned conditions. The cellulose wall covered with the obtained MPC content fusibility cellulosic was made into the example 2-1 to 2-3, respectively. When the these-covered cellulose wall was often dried and the front face was analyzed by ESCA, the peak of the Lynn atom which originates in an MPC unit in all samples, and a nitrogen atom was accepted.

[0040] 1g [of copolymers], and 1,4-butanediol diglycidyl ether 21mg obtained in 1g of copolymers obtained in the example 2-1 of a comparison - the example 5 of 2-3 composition, and the example 6 of hexamethylenediamine 12mg; composition; 1g [of copolymers] and 1,4-butanediol jig SHIJIRU ether 21mg obtained in the synthetic example 7 was dissolved in ethanol 20ml, respectively, and the cast film was produced by applying to rinsing and the cellulose film (10cmx10cm) which carried out the air dried, and drying it beforehand The cellulose wall covered with the copolymer given in JP,7-184989,A was obtained by heating each cast film at 80 degrees C for 2 hours. When the front face was analyzed by ESCA by making these into the example 2-1 to 2-3 of a comparison, respectively, the peak of the Lynn atom which originates in an MPC unit in all samples, and a nitrogen atom was accepted.

[0041] It was immersed in the solution which dissolved each of the copolymer obtained in the example 2-4 of a comparison - the examples 8-10 of 2-6 composition in the ethanol solution so that it might become the concentration of 5 weight / capacity % for about 1 minute, and it was made to dry beforehand rinsing and the cellulose film (10cmx10cm) which carried out the air dried with a 30-degree C forced-air drier, respectively. After repeating this actuation 3 times, the cellulose wall covered with the copolymer given in JP,7-184990,A was obtained by heating at 140 degrees C for 2 hours. When the front face was analyzed by ESCA by making these into the example 2-4 to 2-6 of a comparison, respectively, the peak of the Lynn atom which originates in an MPC unit in all samples, and a nitrogen atom was accepted.

[0042] 100ml of dehydrated methylene chlorides was added to 0.68g [of copolymer solutions obtained in the example 11 of example of comparison 2-7 composition], and dicyclohexylcarbodiimide 1.91g, and 4-(dimethylamino) pyridine 1.5mg, and it dissolved. Subsequently, after making an acetone beforehand immersed in the obtained solution, the cellulose film (10cmx10cm) which carried out the air dried was made immersed for 24 hours. Then, after washing by making a methanol immersed (x during 10 minutes 3 times), the cellulose wall covered with the macromolecule acid given in JP,7-231935,A was obtained by being air-dry. When the front face was analyzed by ESCA by making this into the example 2-7 of a comparison, the peak of the Lynn atom resulting from an MPC unit and a nitrogen

atom was accepted.

[0043] After immersing the film produced in the <haemocompatibility evaluation> example 3, example of comparison 3 example 2-1 to 2-3 (example 3), and the example 2-1 to 2-7 (example 3 of a comparison) of a comparison in a phosphate buffer solution (PBS) for one day, respectively and removing PBS, 0.7ml of rabbit platelet rich plasma was contacted for 180 minutes at the room temperature. Next, plasma was removed with the aspirator and 1.0ml of glutaraldehyde solutions was contacted for 120 minutes 2.5% of the weight after 3 times washing by PBS. Then, the glutaraldehyde solution was removed with the aspirator, after distilled water washed 4 times, it freeze-dried, and the vacuum drying was further put in and carried out to the desiccator on the 1st. When the front face of each obtained cellulose wall was observed with the scanning electron microscope, most platelets had adhered in no samples.

[0044] After performing the processing same to example of comparison 4 a non-processed cellulose film as an example 3, when the membranous front face was observed with the scanning electron microscope, 130,000 platelets /of 2 had adhered mm.

[0045] 60ml of 2mg [/ml] urea water solutions and 60ml of distilled water which dissolved with distilled water were put into coincidence at each glass cell so that it may be in the condition of having divided with the film obtained in the <solute permeability experiment> example 4, example of comparison 5 example 2-1 to 2-3 (example 4), and the example 2-1 to 2-7 (example 5 of a comparison) of a comparison. 0.5ml was extracted from the cel by the side of distilled water every 20 minutes, agitating, and the penetrable experiment of 2 hours was conducted. The quantum of a urea extracted 0.02ml of specimens, and performed them by the calibration-curve method in the standard water solution of a urea using the measurement kit of urea nitrogen B-Test Wako (urease indophenol method) (product made from Wako Pure Chem Industry). A result is shown in Table 2. Moreover, the result similarly performed using the unsettled film is also collectively shown in Table 2. The result of Table 2 shows practically that membranous penetrable ability is maintained in the fusibility cellulose covering cellulose wall of this invention. On the other hand, the high polymer of the gel who generated the film obtained in the example 2-1 to 2-6 of a comparison on the film front face became a failure, and membrane permeability fell remarkably.

[0046]

[Table 2]

	透過した尿素量 (mg)					
時間(分)	20	40	60	80	100	120
実施例2−1	0. 6	0. 8	1. 7	2. 5	3. 0	4. 0
実施例2−2	0. 7	1. 0	1. 9	2. 6	3. 1	4. 0
実施例2−3	0. 9	1. 2	2. 0	2. 6	3. 0	4. 1
比較例2−1	0. 1	0. 2	0. 4	0. 6	0. 7	0. 8
比較例2−2	0. 0	0. 2	0. 3	0. 5	0. 6	0. 7
比較例2−3	0. 1	0. 2	0. 3	0. 6	0. 8	1. 0
比較例2−4	0. 2	0. 3	0. 4	0. 7	0. 9	1. 1
比較例2−5	0. 1	0. 2	0. 4	0. 6	0. 7	0. 8
比較例2−6	0. 2	0. 3	0. 5	0. 7	0. 9	1. 0
比較例2−7	0. 4	0. 7	1. 2	2. 2	2. 8	3. 8
未処理	1. 1	1. 4	2. 2	2. 9	3. 3	4. 3

[0047] The film obtained in the <elution test> example 5, example of comparison 6 example 2-1 to 2-3 (example 5), and the example 2-1 to 2-7 (example 6 of a comparison) of a comparison was immersed in 10ml of each solvent of distilled water and ethanol at the room temperature for 3 hours, and the elution volume of a polymer was calculated by carrying out the quantum of the Lynn content in a solution. Moreover, the amount of polymers which the cellulose wall was made to cover beforehand was calculated by the quantum of Lynn, and the rate of elution of a polymer was computed from this value and elution volume. A result is shown in Table 3. From the result of Table 3, the regenerated-cellulose system film of this invention was hardly accepted for neither of elution of a polymer into water and ethanol. The film obtained on the other hand in the example 2-1 to 2-7 of a comparison had the high elution volume of a polymer compared with the cellulose wall of this invention, and the inclination is ethanol especially had the remarkable solvent.

[0048]

[Table 3]

ID=000004

[Translation done.]